IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application of:
Alfonso ROMERO et al.

Application No.:	10/594,004	Confirmation No.:	8959
Filed:	September 25, 2006	Art Unit:	1616
For:	PROLONGED-RELEASE COMPOSITIONS COMPRISING TORASEMIDE AND A MATRIX-FORMING POLYMER	Examiner:	Abigail Fisher

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Antonio GUGLIETTA, declare and say as follows:

I am an inventor in the present application and I am familiar with U.S. Application No. 10/594,004.

The experiments discussed herein were conducted under my supervision and control.

The following test data shows that the inherent crystallinity of the Torasemide [e.g. in the tablets of Examples 6-9 of the present application] is not affected by the process used to make the tablet.

Discussion

Aim

The aim of this study is to verify the crystallinity of Torasemide (drug substance) in the tablets of Examples 6-9 of US patent application No. 10/594,004.
The tablets of Example 9 correspond to the commercial drug product (Sutrilneo). Torasemide is produced in the polymorphic form I.

The morphology of Torasemide in the pill was characterised using X-Ray Powder Diffraction (XRPD).

Experimental

Four samples were provided to the XRPD group from the Scientific-Technical Service of the University of Barcelona (SCT-UB). These samples were:

- PILL Torasemide: commercial pill Sutrilneo 5 mg, batch E009. It was broken carefully with a metallic spatula for the analysis.
- MIX Torasemide: the same composition of the PILL Torasemide (see Table 1) prepared in the laboratory.
- MIX Placebo: same mixture as MIX Torasemide, but without Torasemide.
- API Torasemide: the drug substance, batch: 1E0419.

The pill composition, drug substance and excipients used for the preparation of the MIX Torasemide and MIX placebo samples are summarised in Table 1.

Table 1. Torasemide pill composition.

Compound	Batch	Amount (mg)
Torasemide	1E0419	20
Lactose	0H0636	180.6
Meyprogat 90	1E0398	13.6
Corn stach	1E0459	123.08
Aerosil 200	9K0826	1.70
Magnesium stearate	0E0415	1.02
Total weight	n.a.	340

These four samples were analysed by XRPD. The results were compared in order to find out whether or not Torasemide was present in the pill in a crystalline form.

The XRPD instrument, procedure and parameters are described in the report provided by the SCT-UB included in the annexes.

Results and discussions

The results were extracted from the report sent by the SCT-UB. The XRPD diagrams for the samples PILL Torasemide, MIX Torasemide, MIX Placebo and API Torasemide were compared (see figures 1, 2 and 3).

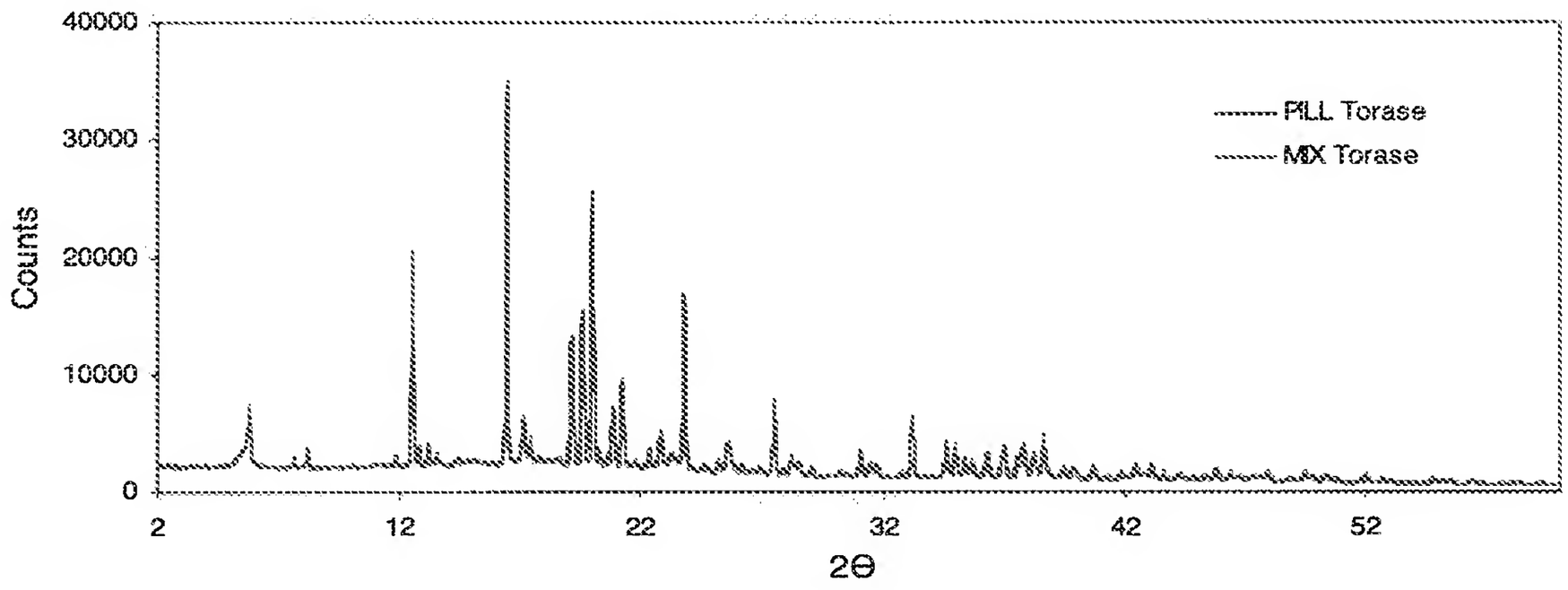

Figure 1. PILL Torasemida and MIX Torasemida diagrams overlaid.

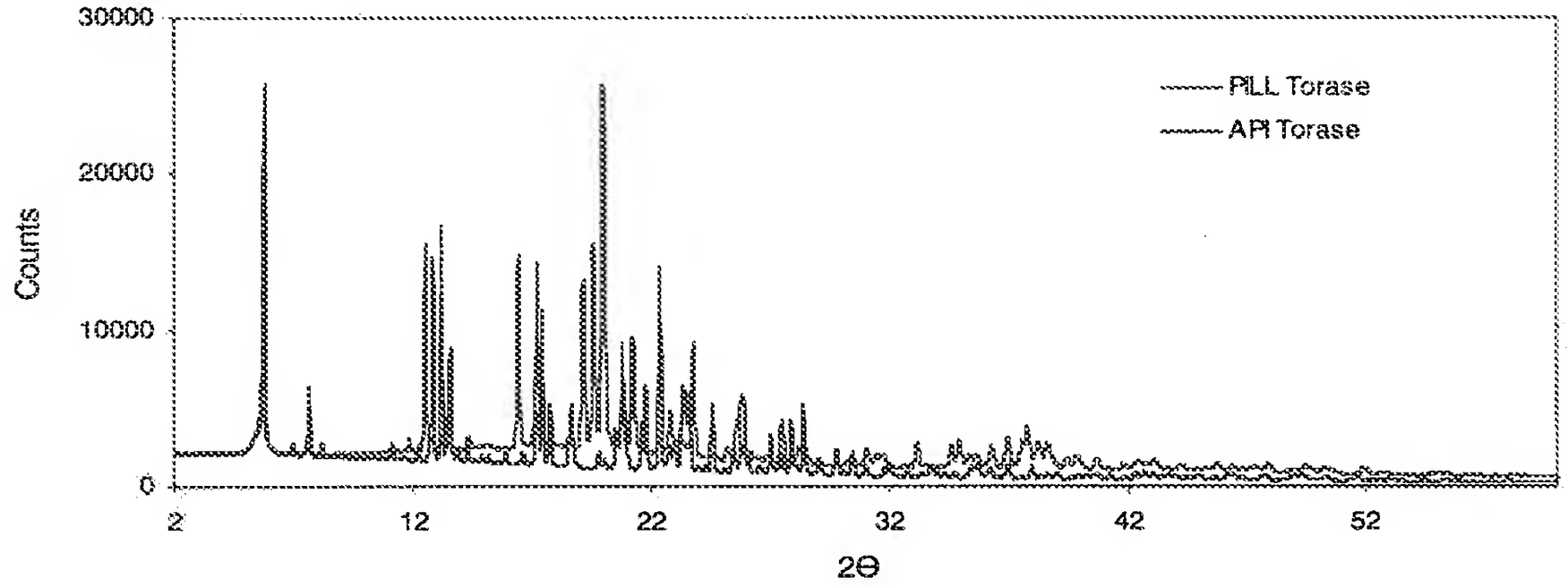

Figure 2. PILL Torasemida and API Torasemida diagrams overlaid.

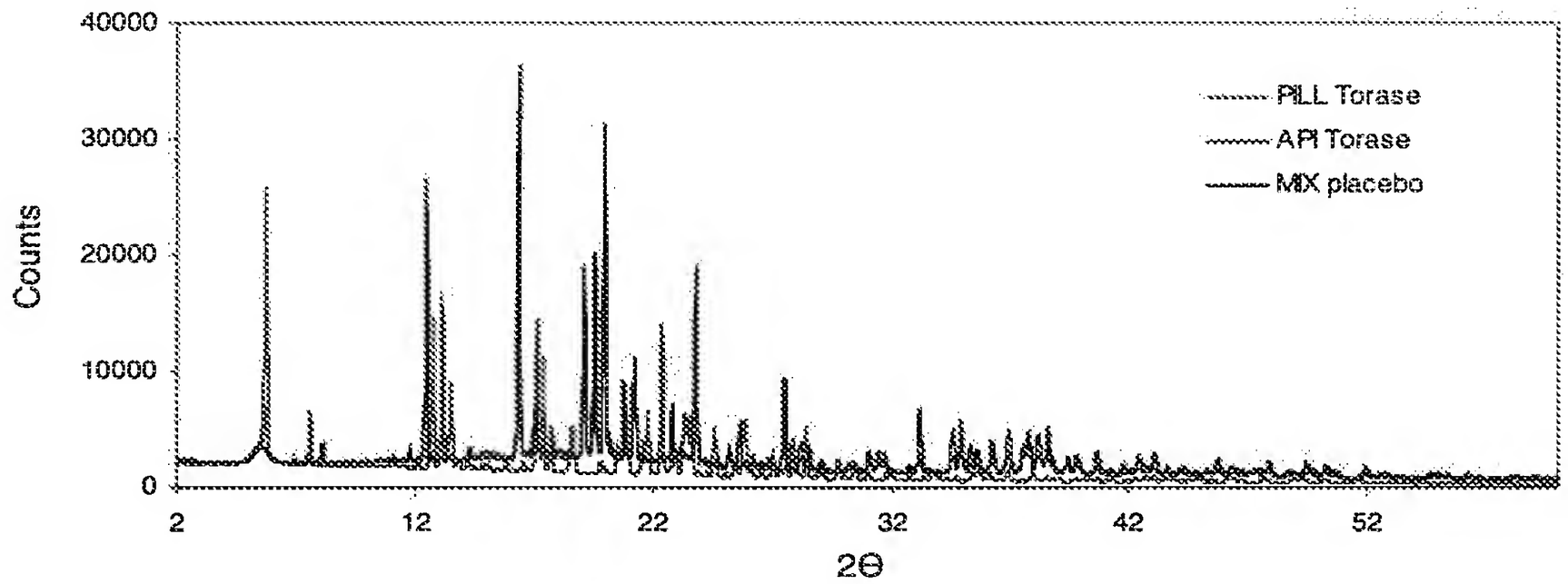

Figure 3. PILL Torasemida, MIX Placebo and API Torasemida diagrams overlaid.

Figure 1 compares the obtained diagrams for the PILL Torasemida and MIX Torasemida samples. The two diagrams show essentially the same patterns. The crystalline phases present in the two samples are the same. Figure 2 compares the obtained diagrams of the samples PILL Torasemida and API Torasemida. The API main peaks are observed also in the pill's diagram. Figure 3 compares the diagrams of PILL Torasemida, API Torasemida and MIX Placebo. The main peaks of the API diagram observed in the pill diagram are not observed in the placebo diagram.

Figures 4 and 5 show some examples of the peaks that appear in the pill and in the API but not in the placebo diagram.

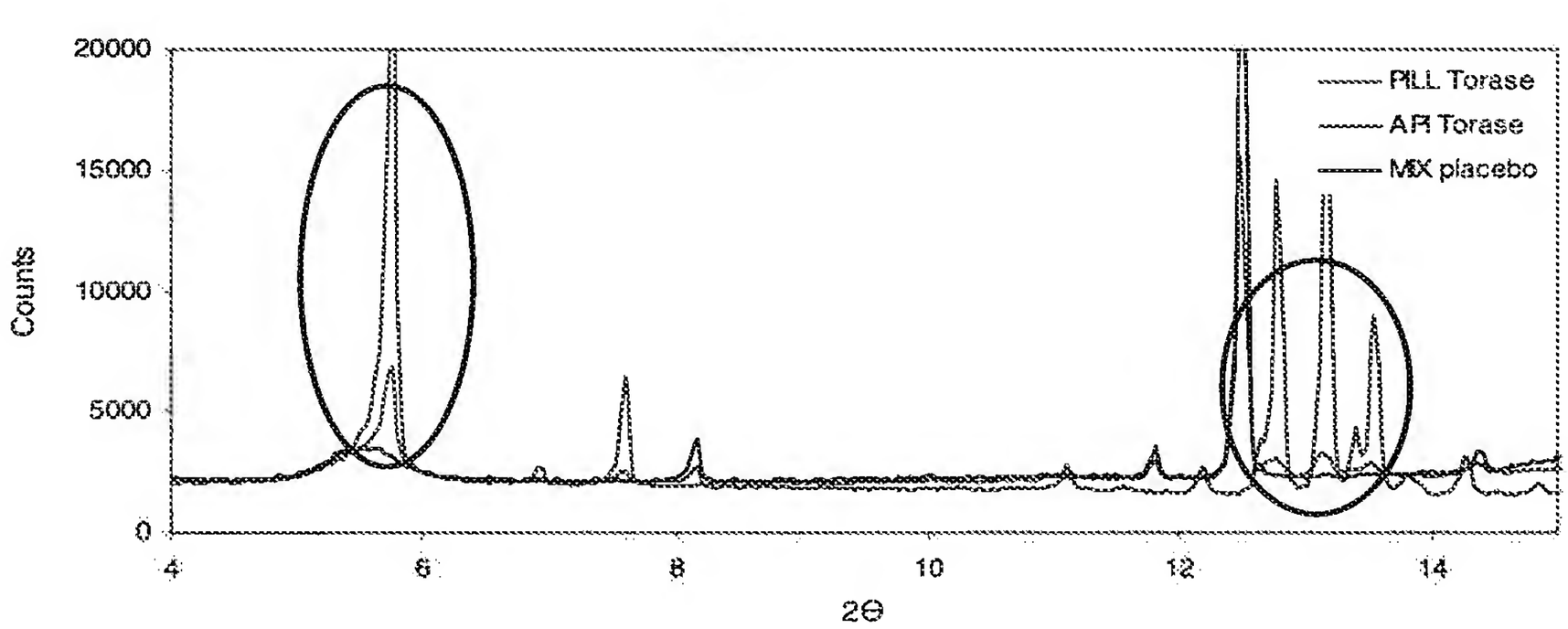

Figure 4. Magnification of the PILL Torasemida, MIX Placebo and API Torasemida diagrams overlaid.

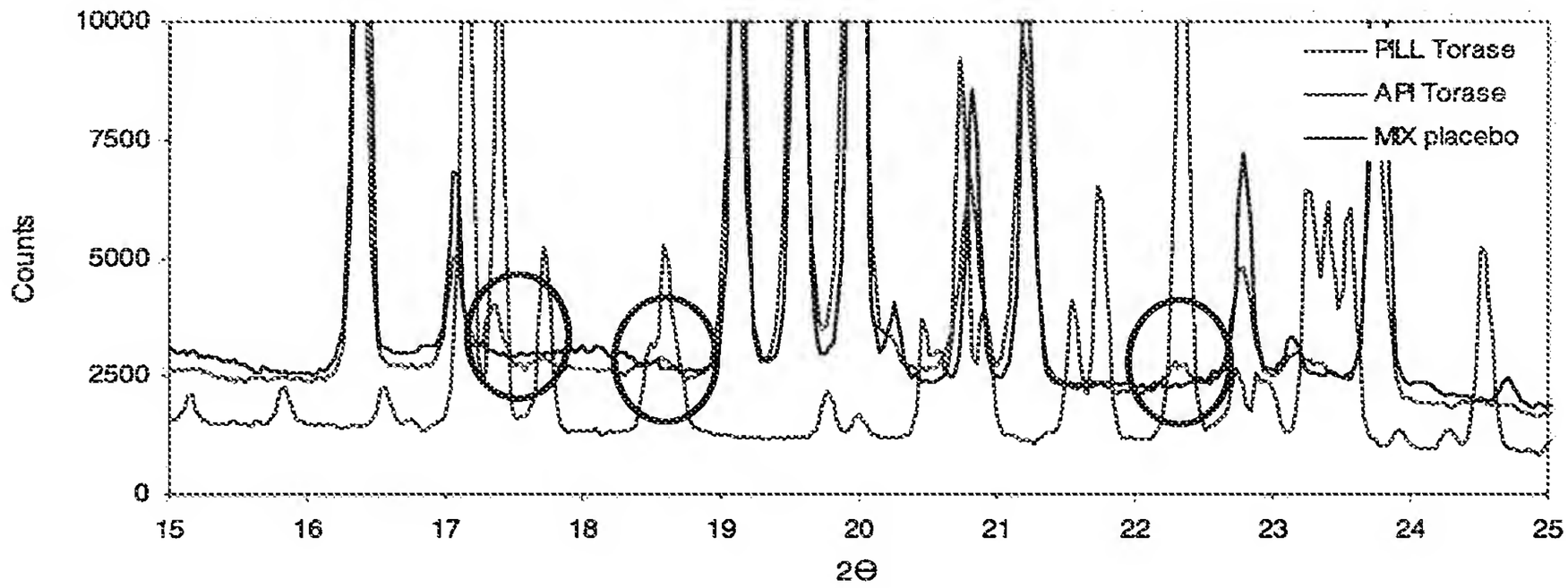

Figure 5. Magnification for the PILL Torasemida, MIX Placebo and API Torasemida diagrams overlaid.

The first circle in figure 4 shows the main peak of Torasemide drug substance, the most intense. This peak appears also in the pill and not in the placebo, indicating the presence of the same crystalline form in the API and in the pill. The second circle is marking a triplete present in the Torasemide drug substance diagram and in the pill, at less intensity, and missing in the placebo. Figure 5 shows the magnification of several peaks that appear in Torasemide drug substance and in the pill, at less intensity.

Figure 6 is a magnification of the diagrams overlaid for the pill, the laboratory mixture and the API. The pill and the laboratory mixture diagrams show some differences in peak intensity. Comparing with the API´s diagram it was observable that the peaks showing higher differences were from the excipients and were not detected in the API´s diagram. The rest of peaks presented in the pill and the laboratory mixture were comparable; therefore, the level of Torasemide´s crystallinity in the pill was substantially the same as observed in the laboratory mixture, prepared with the crystalline API.

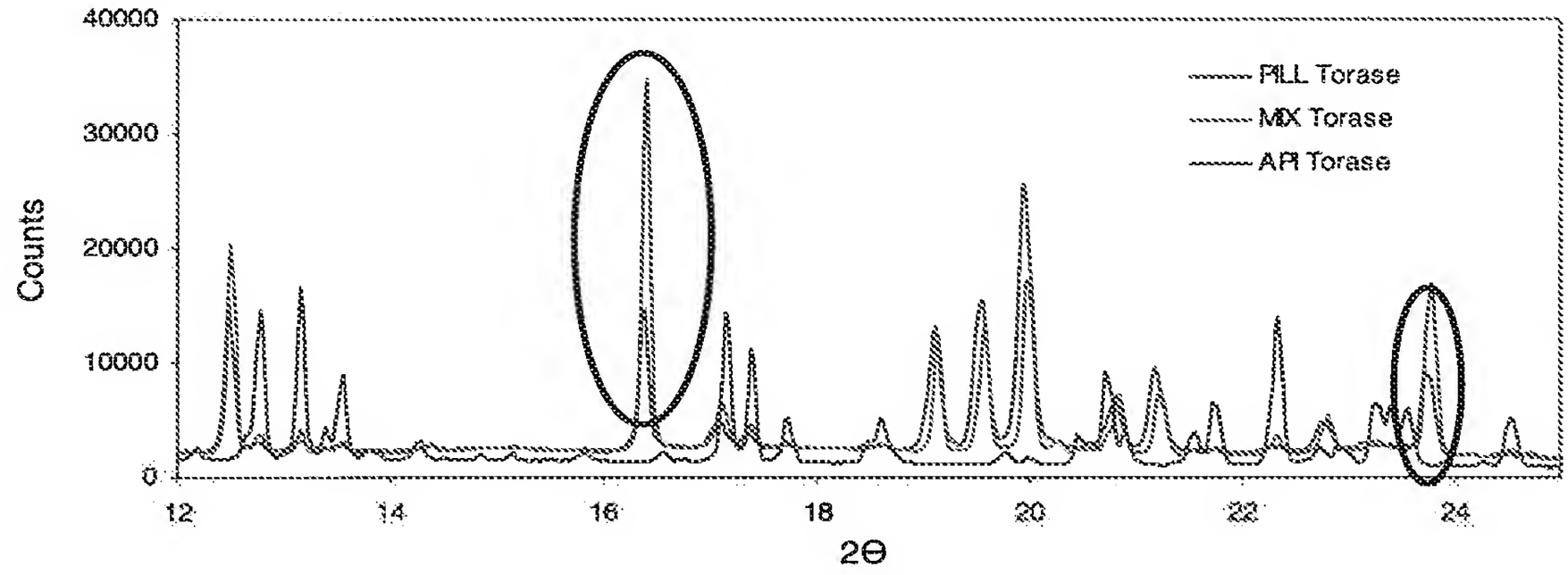

Figure 6. Magnification for the PILL Torasemida, MIX Torasemida and API Torasemida diagrams overlaid. Circled

It is demonstrated that the Torasemide drug substance contained in the pill Sutrilneo 5 mg is crystalline, and it has the same crystalline form than the Torasemide drug substance (batch: 1E0419).

The results from the XRPD analyses makes it unnecessary to perform additional DSC analyses, as the protocol states.

Conclusions

From the XRPD results, it can be concluded that the crystalline form of the Torasemide contained in the pill Sutrilneo 5 mg (batch E009) corresponds to the polymorph form I, the same as for the Torasemide drug substance (batch: 1E0419). More specifically, our data shows that the Torasemide used in the invention is inherently crystalline. Accordingly, it is clear that the active ingredient in the tablets of Examples 6-9 is still in crystalline form and not destroyed by the process of making the tablets in the Examples. As such, the present compositions [e.g. in the tablets of Examples 6-9] are crystalline, which is distinct from US 2003/0153608A1 to Maegerlein et al., which teaches compositions comprising torasemide in "essentially noncrystalline form."

ANNEXES

Annex 1. Final report provided by the SCT-UB.

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PNT 2090143 DOC/006 Ed. 9. Annex VII

REGISTRY Num. 03953/2011

Mr. Jaume SEUMA
FERRER INTERNACIONAL, S.A.
C/ Joan de Sada, 32
08028 Barcelona

Analysed samples

Description:	Four powder solid samples related to the pharmaceutical product *Torasemide*	
References	User	DRX
	MIX Torasemida	*03953/2011-1*
	MIX Placebo	*03953/2011-2*
	PILL Torasemida	*03953/2011-3*
	API Torasemida	*03953/2011-4*
Performed experiments:	X-ray powder diffraction analysis	
Date of sample reception:	11-X-2011	
Date of the experiments:	18-X-2011	

Methodology

Sample preparation:

The samples were sandwiched between polyamide (*Kapton*) films of 15 microns of thickness.

Instrument and experimental conditions:

PANalytical X'Pert PRO MPD θ/θ powder diffractometer of 240 millimetres of radius, in a configuration of convergent beam with a focalizing mirror and a transmission geometry with flat samples sandwiched between low absorbing films
Cu Kα radiation (λ = 1.5418 Å).
Work power: 45 kV – 40 mA.
Incident beam slits defining a beam height of 0.4 millimetres
Incident and diffracted beam 0.02 radians *Soller* slits
PIXcel detector: Active length = 3.347 °.
2θ scans from 2 to 60 °2θ with a step size of 0.026 °2θ and a measuring time of 200 seconds per step

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Objectives

The sample *API Torasemida* is a powder sample of the API pharmaceutical product *Torasemide*. The sample *PILL Torasemida* is a pharmaceutical speciality, a pill, containing a 5 % in weight of the API pharmaceutical product *Torasemide*. The sample *MIX Torasemide* is a powder mixture with the same components than in the pill pharmaceutical speciality. The sample *MIX Placebo* is a powder mixture with the same components than in the pill pharmaceutical speciality but without the API pharmaceutical product *Torasemide*.

The objective of the study is to determine if the API pharmaceutical product *Torasemide* in the pill pharmaceutical speciality *PILL Torasemida* is or not crystalline and in the case of being crystalline determine if the crystalline form is or not the same than the one in the powder sample of the API pharmaceutical product.

Results

Figure 1, 2, 3 and 4 depict the obtained X-ray powder diffraction diagrams in the main angular range from 2 to 40 °2θ.

Figure 5 compares the obtained diagrams of the samples *PILL Torasemida* and *MIX Torasemida*. The two diagrams are essentially the same. The crystalline phases present in the two samples are the same. Figure 6 compares the obtained diagrams of the samples *PILL Torasemida* and *API Torasemida*. All the main peaks in the *API Torasemida* sample diagram are observed in the *PILL Torasemida* sample diagram. Figure 7 compares the diagrams of the samples *PILL Torasemida*, *API Torasemida* and *MIX Placebo*. The main peaks of the *API Torasemida* sample diagram observed in the *PILL Torasemida* sample diagram are not observed in the *MIX Placebo* sample diagram. It is clear that the API pharmaceutical product *Torasemide* in the pill pharmaceutical speciality *PILL Torasemida* is crystalline and that the crystalline form is the same than the one in the powder sample of the API pharmaceutical product.

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Figure 1: 'API Tenosmide'

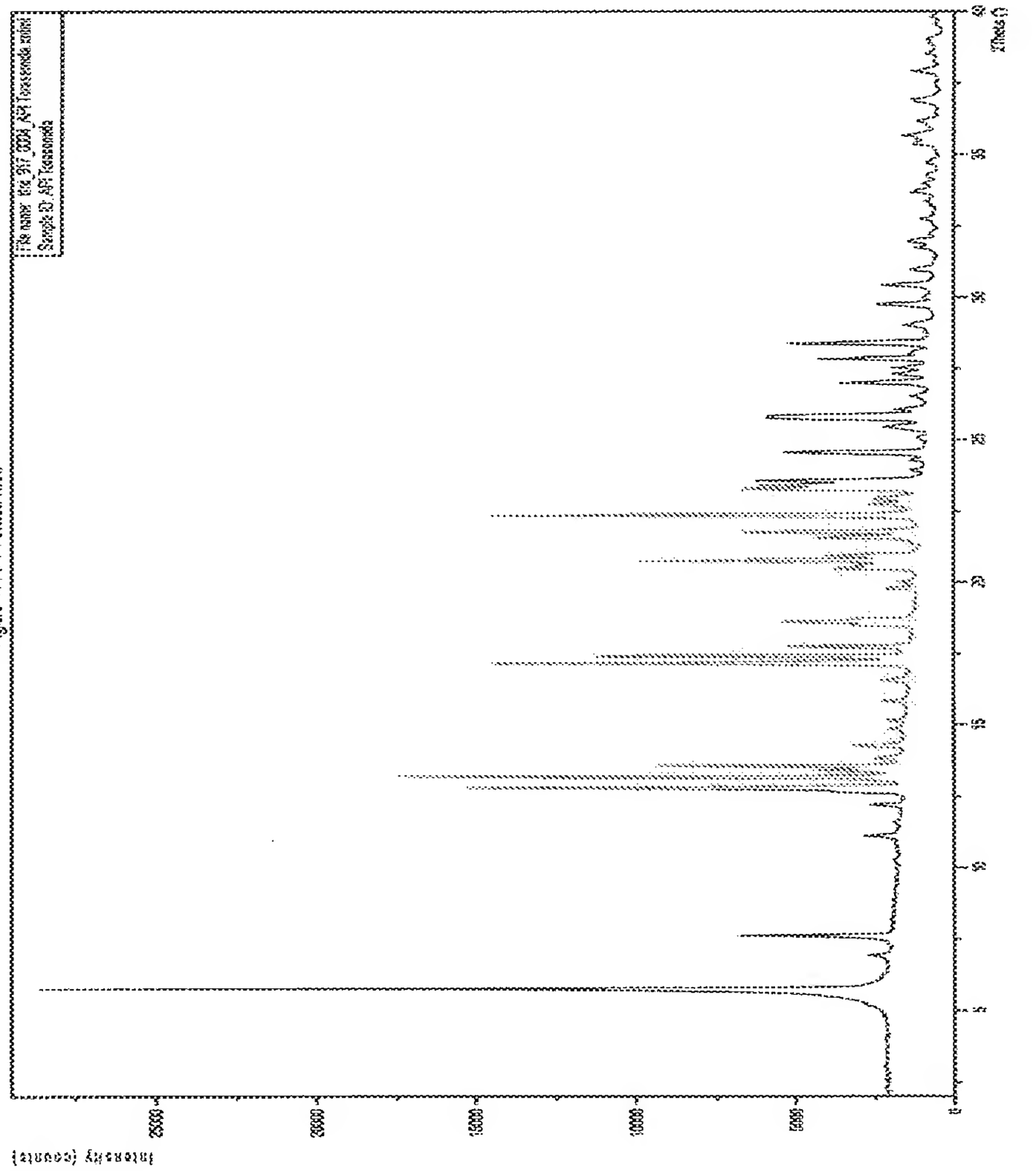

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Figure 2: PLL Tetrasemide

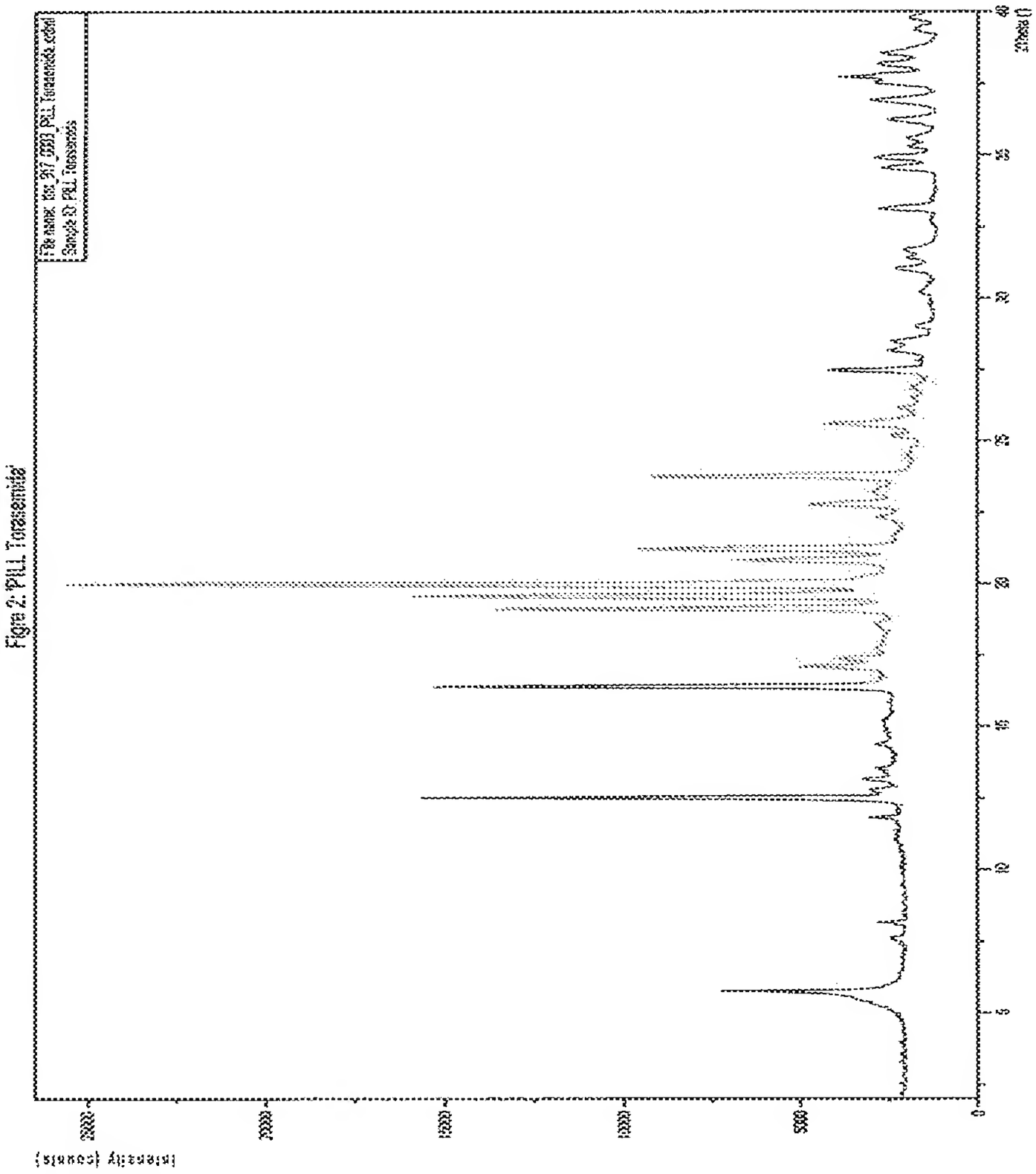

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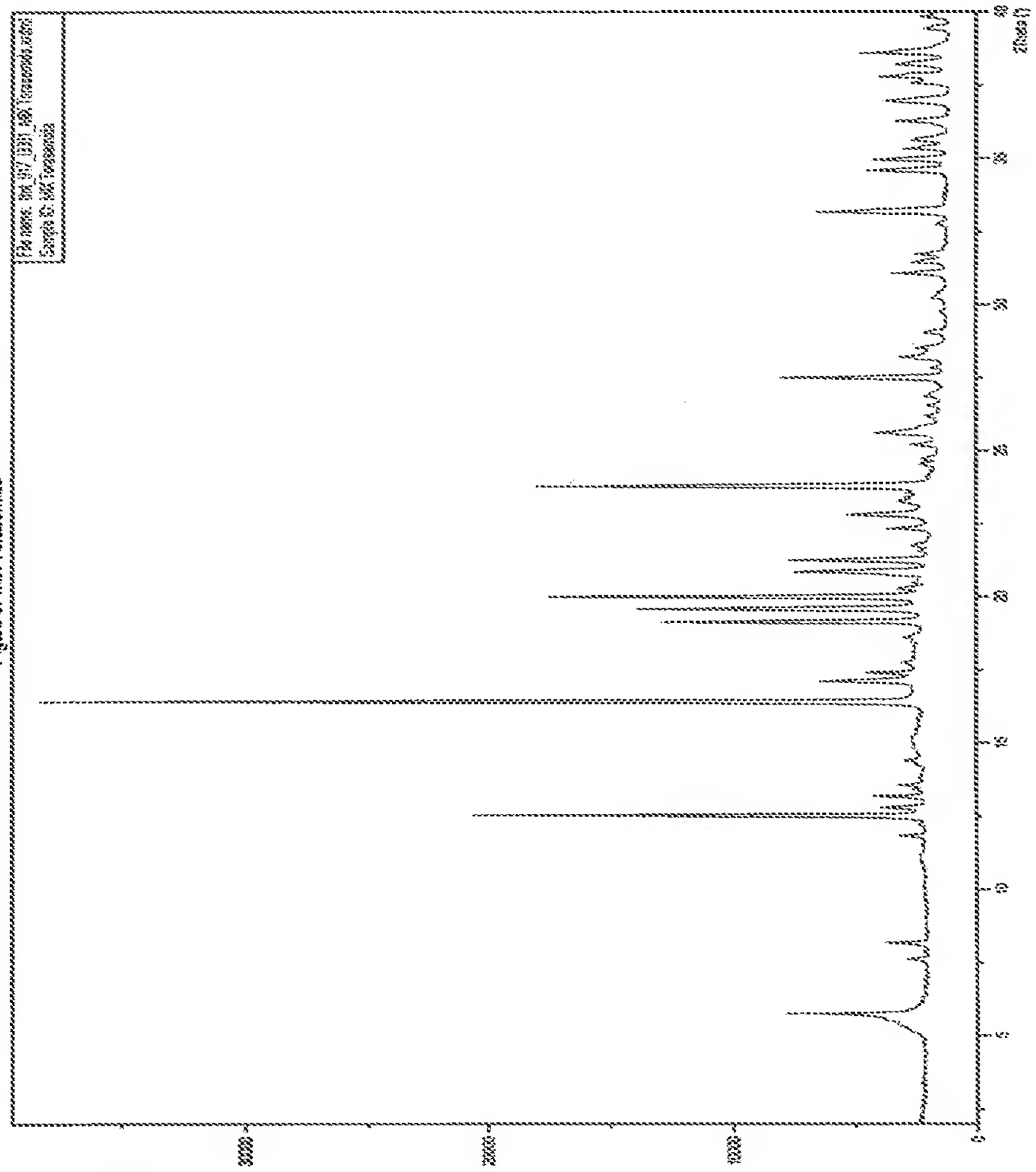
Figure 3: 'MIX Torasemide'



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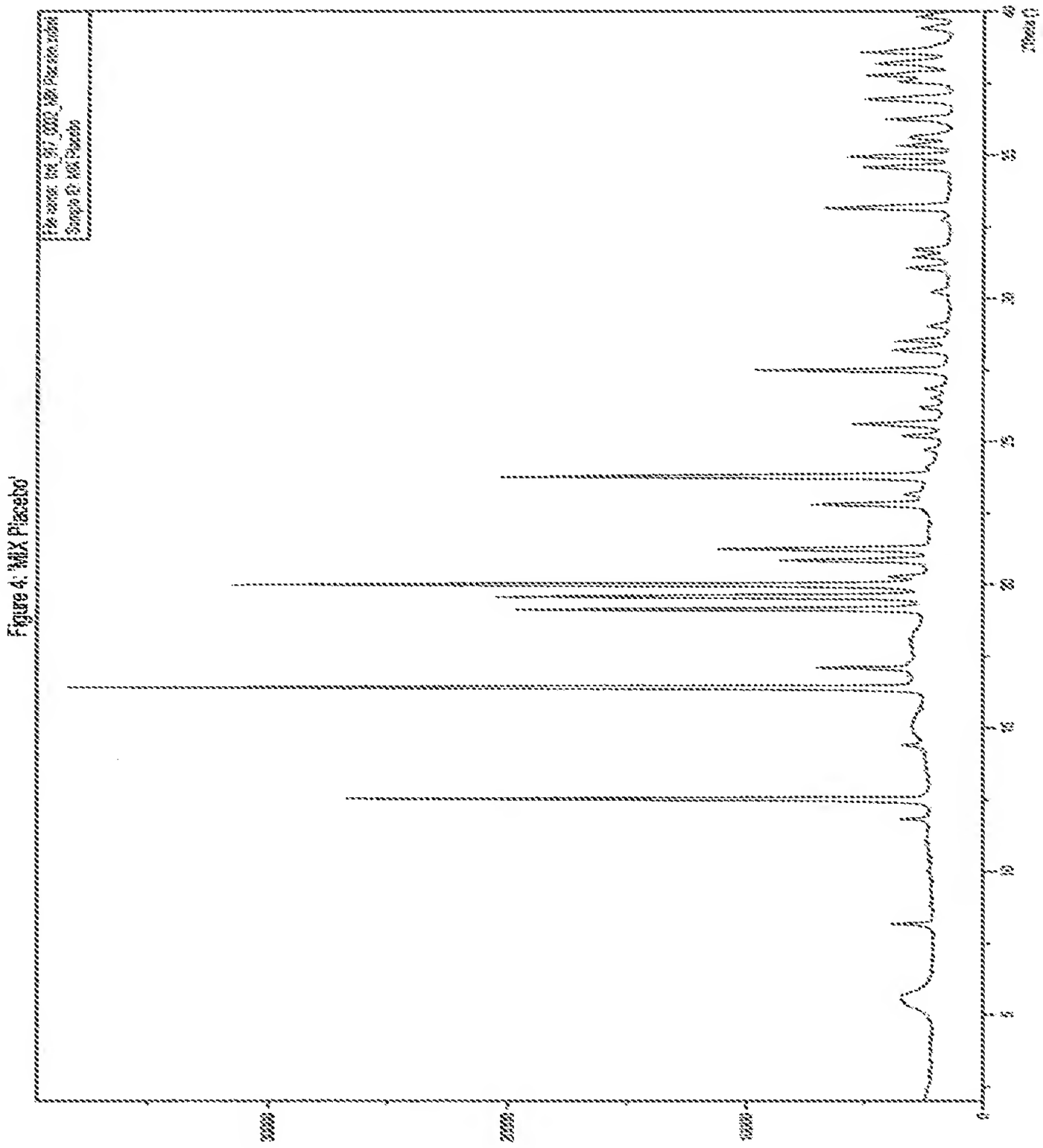

Figure 4: MRX Placebo

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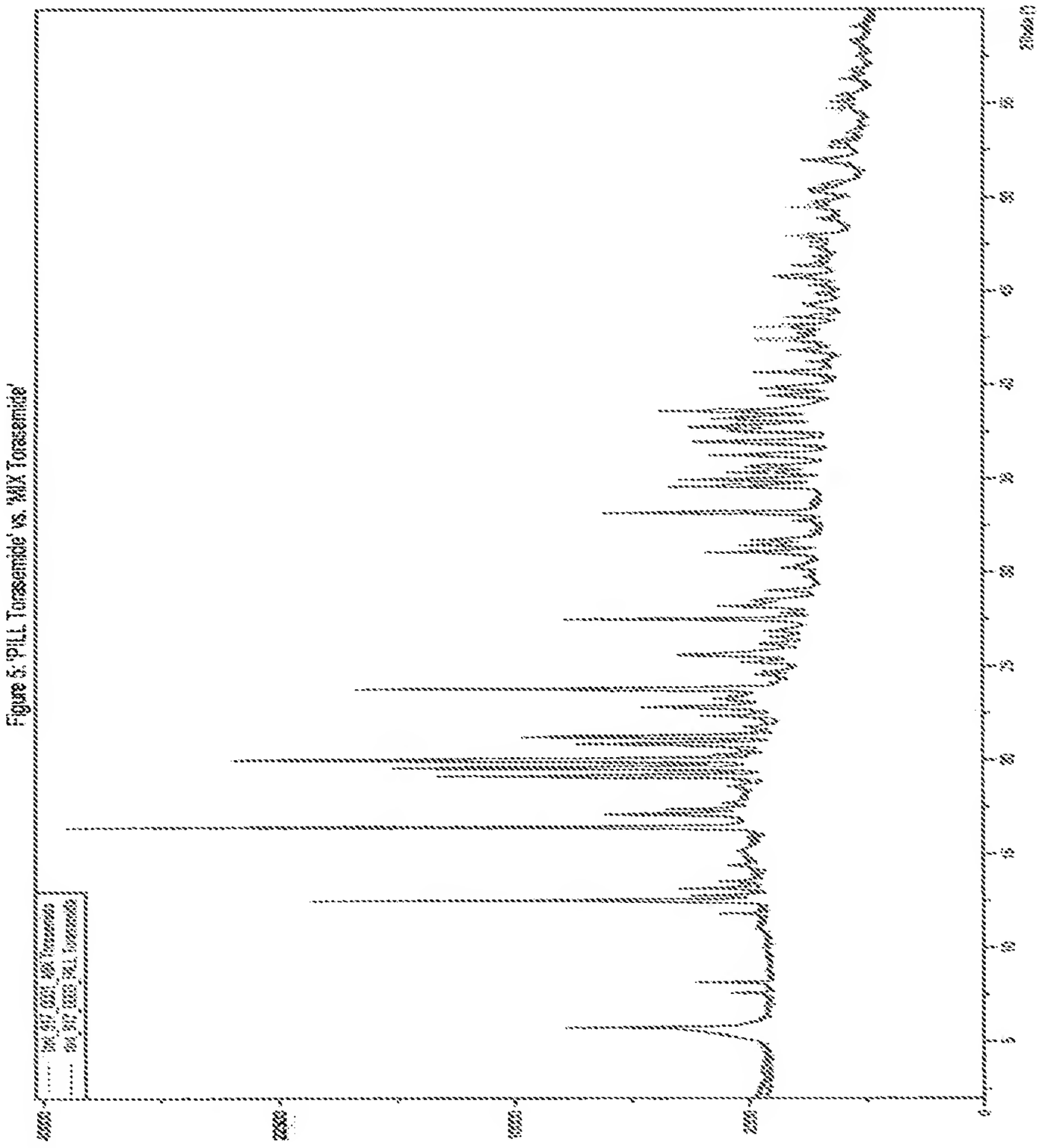
Figure 5: 'PILL Torasemide' vs. 'MIX Torasemide'



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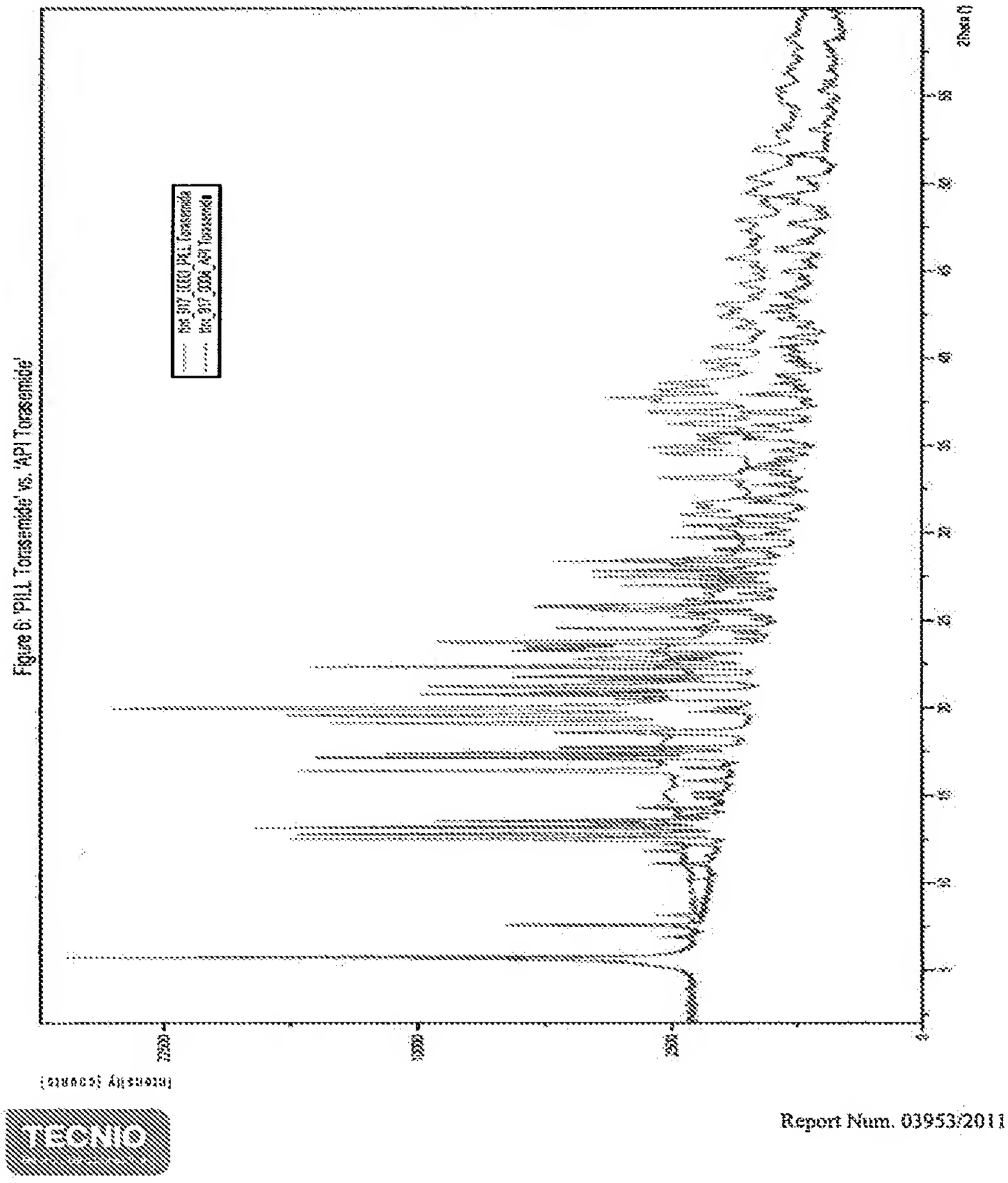

Figure 6: 'PILL Torasemide' vs. 'API Torasemide'

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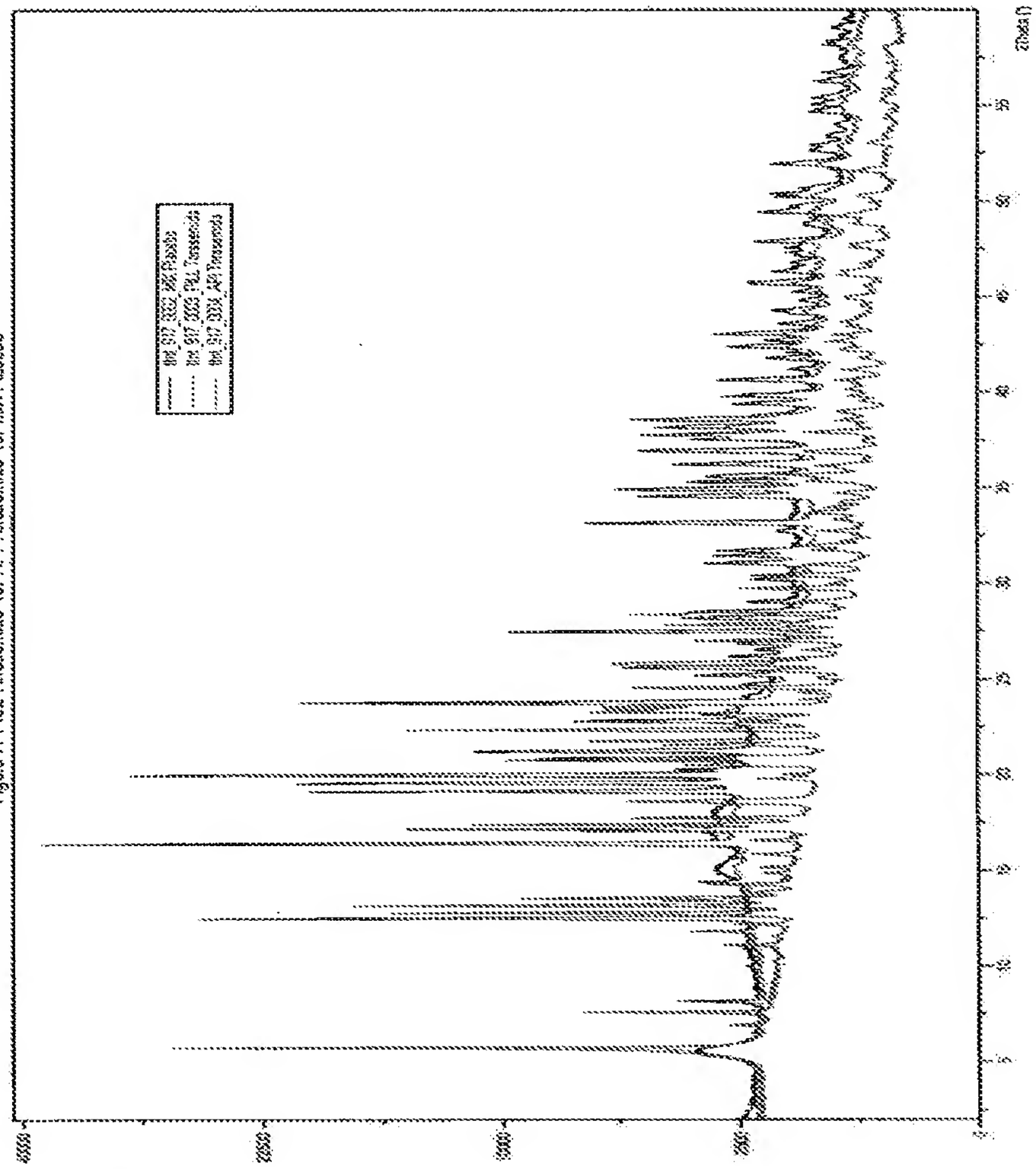

Figura 7: 'Pkl Torasemida' vs. 'API Torasemida' vs. 'XRX Placebo'

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Barcelona, 31st October 2011

Dr. Xavier Alcobé Ollé
Head of the X-ray Diffraction Department

- The results refer only to the samples analysed.
- This report cannot be reproduced partially without prior written consent by the Scientific-Technical Services.
- The samples will be kept for a period of three months after releasing this report, and will be destroyed thereafter. The primary results will be kept for five years.
- The Scientific-Tecchnical Services has a Quality Management System certified in accordance with the standard ISO 9001 by APPLUS.

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Annex 2. Certificate of Analysis of Torasemide (see table 1).

ferrer

Ferrer Internacional S.A.
Planta Especialidades Farmacéuticas
Joan Buscallà 1-9
08173 Sant Cugat del Vallés
Barcelona - España / Spain

Certificate of analysis

Material:	MICROCRYSTALLINE TORASEMIDE				
Material code:	3003379			Batch:	1E0419
Amount:	60000,000 G	Supplier:	MEDA AB	Manufacturing date:	04-2010
		Supplier batch:	MH10065006	Retest date:	04-2013

Components	Result	Requirements
ANALYTIC CERTIFICATE RECEPTION	PASS	CERTIFICATE RECEIVED

Analysis date: 16-05-2011
Status: COMPLIES
Responsable: Montse Planells

Specification: 3003379 (M) TORASEMIDA MICROCRIST. (ger/ver: 1/1)

Electronically generated certificate, valid without signature
Complies Ph. Eur. requirements
Certificado_compp_FISA_mt.rep / 20101214

COPIA AUTÉNTICA
Fecha: 10/10/11
Firma:

Ferrer Internacional S.A.
Planta Especialidades Farmaceuticas
Joan Buscallà 1-9
08173 Sant Cugat del Vallés
Barcelona - España / Spain

Certificate of analysis

Material:	MICROCRYSTALLINE TORASEMIDE				
Material code:	3003379			Batch:	100327
Amount:	60000,000 G	Supplier:	ROCHE DIAGNOSTICS	Manufacturing date	04-2010
		Supplier batch:	MH10065006	Retest date:	04-2013

Components	Result	Requirements
PHYSICAL-CHEMICAL CONTROL		
APPEARANCE	PASS	WHITE OR ALMOST WHITE POWDER
IDENTIFICATION		
IR IDENTIFICATION	POSITIVE	RESPECT STANDARD BY IR
X RAYS IDENTIFICATION	POSITIVE	POLYMORPHIC FORM I
TESTS		
HEAVY METALS	PASS	<=10 (ppm)
SULPHATED ASH	0	<=0.1 (%)
LOSS ON DRYING	.1	<=0.5 (%)
PARTICLE SIZE		
PARTICLE SIZE <12 µm	PASS	>=50 (%)
PARTICLE SIZE <24 µm	PASS	>=90 (%)
PARTICLE SIZE <48 µm	PASS	>=99 (%)
SUSTANCIA RELACIONADAS (HPLC)		
IMPURITY A	<0.05	<= 0.1 (%)
IMPURITY B	0.2	<= 0.5 (%)
IMPURITY C	0.1	<= 0.1 (%)
IMPURITY D	NOT DETECTED	<= 0.1 (%)
ANY OTHER IMPURITY	<0.05	<=0.1 (%)
TOTAL IMPURITIES	0.3	<=0.6 (%)
ASSAY		
POTENTIOMETRIC TITRATION (ANHYDROUS	101.0	99.0 - 101.0 (ANHYDROUS SUBSTANCE) (%)
TRIETILAMINA (CG)		
TRIETHYLAMINE	<320	<=320 (ppm)

Analysis date: 03-05-2011
Status: COMPLIES
Responsable: Montse Planells

Specification: 3003379 TORASEMIDA MICROCRISTALINA (gen/ver: 13/1)

Electronically generated certificate, valid without signature
Complies Ph. Eur. requirements
Certificado_rempp_FISA_mtrep / 20101214

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Original en CRD

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Roche

Safety Data Sheet

Torasemide

1. Product and Company Identification

Product name	Torasemide
Product code	04 7523 8
Company information	Enquiries: F. Hoffmann-La Roche AG Postfach CH-4070 Basel Switzerland Phone *41-61/688 54 80 Fax *41-61/691 72 76 Local representation:

2. Composition/Information on Ingredients

Characterization	pharmaceutical active substance
Chemical name	- N-[[(1-Methylethyl)amino]carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide
CAS number	56211-40-6
Empirical formula	$C_{16}H_{20}N_4O_3S$
Molecular mass	348.46 g/mol

3. Hazards Identification

Most important hazards	- No particular hazards known.

4. First-aid measures

Eye contact	- rinse immediately with tap water for 10 minutes - open eyelids forcibly - consult physician
Skin contact	- remove contaminated clothes, wash affected skin with water and soap - do not use any solvents
Inhalation	- remove the casualty to fresh air and keep him/her calm - consult physician
Note to physician	- treat symptomatically

Date: 7.4.99/CSE (SEISMO) Replacing edition of: - Page: 1/5

Torasemide

5. Fire-fighting measures

Suitable extinguishing media	- water spray jet, dry powder, foam, carbon dioxide
Unsuitable extinguishing media	- full water jet
Specific hazards	- formation of toxic and corrosive combustion gases (nitrogen oxides, sulfur oxides) possible - Material is combustible
Protection of fire-fighters	- precipitate gases/vapours/mists with water spray - use self-contained breathing apparatus

6. Accidental release measures

Personal precautions	- evacuate area, remove sources of ignition, ventilate
Environmental protection	- do not allow to enter drains or waterways - avoid release to the environment
Methods for cleaning up	- collect solids (avoid dust formation) and hand over to waste removal

7. Handling and storage

Handling

Technical measures	- processing in closed systems, if possible superposed by inert gas (e.g. nitrogen) - take precautionary measures against electrostatic charging - avoid dust formation
Suitable materials	- stainless steel, glass, aluminium, enamel

Storage

Storage conditions	- no special measures or restrictions for storage known
Packaging materials	- tightly closing

8. Exposure controls/Personal protection

Engineering Measures	- see 7.

Personal protective equipment:

Respiratory protection	- in case of open handling or accidental release: particle mask or respirator with independent air supply
Hand protection	- protective gloves
Eye protection	- safety glasses

Torasemide

9. Physical and chemical properties

Colour	white
Form	solid
Odour	odourless
Solubility	badly soluble, water
Melting temperature	157 to 164 °C

10. Stability and reactivity

Stability	- stable under the conditions mentioned in chapter 7

11. Toxicological information

Acute toxicity	- LD_{50}	> 5'000	mg/kg	(oral, rat)
	- LD_{50}	> 500	mg/kg	(i.v., rat)
Note	- diuretic			

12. Ecological information

Air pollution	- observe local/national regulations
Note	- no ecotoxicological data available on this compound

13. Disposal considerations

Waste from residues	- observe local/national regulations regarding waste disposal - incinerate in qualified installation with flue gas scrubbing

14. Transport information

Note	- not classified by transport regulations

15. Regulatory information

Note	- no classification and labelling according to EU
Water hazard class (Germany)	2: hazardous for water (own classification according to directive VwVwS of 17.05.1999)

16. Other information

Edition documentation	first edition

The information in this safety data sheet is based on current scientific knowledge. It should not be taken as expressing or implying any warranty concerning product characteristics.

Annex 3. Certificate of Analysis of Aerosil 200 (see table 1).

Ferrer Internacional S.A.
Planta Especialidades Farmaceuticas
Joan Buscalla 1-9
08173 Sant Cugat del Vallès
Barcelona - España / Spain

Certificado de análisis

Producto: AEROSIL 200

Código producto: 3000021 Lote: 9K0826

Cantidad: 450000,000 G Proveedor: IMPEX QUIMICA S.A. Fecha fabricación: 11-2008

Lote proveedor: 3159091614 Fecha retest: 12-2012

Determinaciones	Resultado	Especificaciones
CONTROL FISICO-QUIMICO		
ASPECTO	CONFORME	POLVO BLANCO O CASI BLANCO, LIGERO, FINO Y AMORFO
IDENTIFICACION SILICATOS	POSITIVA	SATISFACE REACCION SILICATOS
ENSAYOS		
pH (USP)	4.7	3.5 - 5.5
pH (Ph. Eur.)	4.5	3.5 - 5.5
CLORUROS	CONFORME	<=250 (ppm)
METALES PESADOS	CONFORME	<=25 (ppm)
PERDIDA POR DESECACION (USP)	.32	<= 2.5 (%)
PERDIDA POR CALCINACION (USP)	.78	<= 2.0 (%)
PERDIDA POR CALCINACION (Ph. Eur.)	.43	<= 5.0 (%)
ARSENICO (USP)	CONFORME	<= 6
VALORACION (GRAVIMETRICA)		
OXIDO DE SILICE (Ph. Eur)	99.5	99.0 - 100.5 (spc.) (%)
OXIDO DE SILICE (USP)	99.9	99.0 - 100.5 (spc.) (%)

Fecha análisis: 04-12-2008 Especificación: 3000021 AEROSIL 200 (genVer: 8/1)

Dictamen: CONFORME

Nº Certificado: 7000665535 / 4

Certificado emitido electrónicamente, es válido sin firma

Cumple requerimientos de Ph. Eur. y USP

Certificado_compq_FISA_ml.rep / 28091231

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Annex 4. Certificate of Analysis of Corn starch (see table 1).

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Ferrer Internacional S.A.
Planta Especialidades Farmacéuticas
Joan Buscallà 1-9
08173 Sant Cugat del Vallès
Barcelona - España / Spain

Certificado de análisis

Producto:	ALMIDON DE MAIZ				
Código producto:	3000031			Lote:	1E0459
Cantidad:	1000000,000 G	Proveedor:	BRENNTAG QUIMICA,S.A.	Fecha fabricación:	02-2010
		Lote proveedor:	01257670	Fecha retest:	02-2013
		Fabricante:	600146 CERESTAR		

Determinaciones	Resultado	Especificaciones
CONTROL FISICO-QUIMICO		
ASPECTO	CONFORME	POLVO MUY FINO, BLANCO O AMARILLENTO
IDENTIFICACION MICROSCOPICA	POSITIVA	PASA TEST
IDENTIFICACION POR CALENTAMIENTO	POSITIVA	PASA TEST
IDENTIFICACION CON IODO	POSITIVA	COLORACION VIOLETA-AZUL
ENSAYOS		
pH	5.4	4.0 - 7.0
ELEMENTOS EXTRAÑOS	CONFORME	PASA TEST
SUSTANCIAS OXIDANTES	CONFORME	<= 20 ppm
DIOXIDO DE AZUFRE	CONFORME	<= 50 (ppm)
HIERRO	CONFORME	<= 10 (ppm)
PERDIDA DE PESO	11	<= 15.0 (%)
CENIZAS SULFURICAS	.2	<= 0.6 (%)
CONTROL MICROBIOLOGICO		
RECUENTO MICROBIOS AEROBIOS TOTALI	40	<= 1 E3 (ufc/g)
RECUENTO MOHOS Y LEVADURAS TOTALI	<10	<= 1 E2 (ufc/g)
ESCHERICHIA COLI	CONFORME	AUSENCIA EN 1 g
SALMONELLA	CONFORME	AUSENCIA EN 10 g

Fecha análisis: 23-06-2011 Especificación: 3000031 ALMIDON DE MAIZ (perVer: 13/1)

Dictamen: CONFORME

Responsable Montse Planells

Certificado emitido electrónicamente, es válido sin firma

Cumple requerimientos de Ph. Eur.

Certificado_monop_FISA_mUsp / 20100216

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Fecha impresión / Print date: 30-06-2011

Annex 5. Certificate of Analysis of Lactose (see table 1).

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Ferrer Internacional S.A.
Planta Especialidades Farmacéuticas
Joan Buscallà 1-9
08173 Sant Cugat del Vallès
Barcelona - España / Spain

Certificado de análisis

Producto:	LACTOSA				
Código producto:	3000263			Lote:	0H0636
Cantidad:	4000000,000 G	Proveedor:	QUIMIDROGA S A	Fecha fabricación:	04-2010
		Lote proveedor:	10512326	Fecha retest:	09-2013
		Fabricante:	600236 DMV		

Determinaciones	Resultado	Especificaciones
CONTROL FISICO-QUIMICO		
ASPECTO	CONFORME	POLVO CRISTALINO BLANCO O PRACTICAMENTE BLANCO
IDENTIFICACION IR	POSITIVA	RESPECTO PATRON POR IR
IDENTIFICACION AGUA	POSITIVA	SATISFACE LOS REQUERIMIENTOS DEL ENSAYO DEL AGUA
ENSAYOS		
ASPECTO DE LA SOLUCION	CONFORME	LIMPIDA Y <= PA7
ACIDEZ O ALCALINIDAD	CONFORME	<= 0.4 ml NaOH 0.1M
ROTACION ESPECIFICA	55	54.4 - 55.9 (spa) (°)
ABSORCION A 400nm	0.01	<=0.04
ABSORCION 210 A 220 nm	0.04	<=0.25
ABSORCION 270 a 300 nm	0.01	<=0.07
METALES PESADOS	CONFORME	<=5 (ppm)
AGUA (K. Fischer)	5.07	4.5 - 5.5 (%)
CENIZAS SULFURICAS	.03	<=0.1 (%)
CONTROL MICROBIOLOGICO		
RECUENTO MICROBIOS AEROBIOS TOTALE	<10	<= 1 E2 (ufc/g)
ESCHERICHIA COLI	CONFORME	AUSENCIA EN 1 g

Fecha análisis: 13-09-2010
Especificación: 3000263 LACTOSA (genVer: 5/1)

Dictamen: CONFORME

Nº Certificado: 700053502 / 1

Certificado emitido electrónicamente, es válido sin firma
Cumple requerimientos de Ph. Eur.
Certificado_mmpp_FISA_ml.rep / 20091201

Annex 6. Certificate of Analysis of Magnesium stereate (see table 1).

ferrer

Ferrer Internacional S.A.
Planta Especialidades Farmacéuticas
Joan Buscallà 1-9
08173 Sant Cugat del Vallès
Barcelona - España / Spain

Certificado de análisis

Producto: ESTEARATO DE MAGNESIO

Código producto: 3000169 Lote: 0E0415

Cantidad: 450000,000 G Proveedor: BRENNTAG QUIMICA,S.A. Fecha fabricación: 03-2009

Lote proveedor: C004537 Fecha retest: 06-2013

Determinaciones	Resultado	Especificaciones
CONTROL FISICO-QUIMICO		
ASPECTO	CONFORME	POLVO BLANCO LIGERO MUY FINO
IDENTIFICACION CG	POSITIVA	TIEMPO DE RETENCION COINCIDE CON PATRON
IDENTIFICACION DE MAGNESIO	POSITIVA	RESPECTO REACCION QUIMICA
ENSAYOS		
ACIDEZ	0	<= 0.05 (ml NaOH 0.1M)
ALCALINIDAD	0.01	<= 0.05 (ml HCl 0.1M)
CLORUROS (USP)	CONFORME	<= 0.1 (%)
CLORUROS (Ph. Eur.)	CONFORME	<= 0.1 (%)
SULFATOS (USP)	CONFORME	<= 1.0 (%)
SULFATOS (Ph. Eur.)	CONFORME	<= 1.0 (%)
CADMIO	CONFORME	SE ASUME DICTAMEN PROVEEDOR <= 3 (ppm)
PLOMO (USP)	CONFORME	<= 10 (ppm)
PLOMO (Ph. Eur)	CONFORME	SE ASUME DICTAMEN PROVEEDOR <= 10 (ppm)
NIQUEL	CONFORME	SE ASUME DICTAMEN PROVEEDOR <= 5 (ppm)
PERDIDA POR DESECACION	2.44	<= 6.0 (%)
VALORACION (VOLUMETRICA)		
MAGNESIO	4.1	4.0 - 5.0 (SOBRE PRODUCTO SECO) (%)
COMPOSICION ACIDOS GRASOS (CG)		
ACIDO ESTEARICO	53.2	>= 40.0 (%)
SUMA AC. ESTARICO Y PALMITICO	98.6	>= 90.0 (%)
CONTROL MICROBIOLOGICO		
RECUENTO MICROBIOS AEROBIOS TOTALE	20	<= 1 E3 (ufc/g)
RECUENTO MOHOS Y LEVADURAS TOTALE	<10	<= 1 E2 (ufc/g)
ESCHERICHIA COLI	CONFORME	AUSENCIA EN 1 g
SALMONELLA	CONFORME	AUSENCIA EN 10 g

Fecha análisis: 15-06-2010 Especificación: 3000169 ESTEARATO DE MAGNESIO (gen/ver: 13/1)

Dictamen: CONFORME

Nº Certificado: 70X0809033 / 1

Certificado emitido electrónicamente, es válido sin firma

Cumple requerimientos de Ph. Eur. y USP

Certificado_rempp_FISA_pt.rep / 20091201 Pág. 1 de 1

Annex 7. Certificate of Analysis of Meyprogat 90 (see table 1).

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Ferrer Internacional S.A.
Planta Especialidades Farmacéuticas
Joan Buscallà 1-9
08173 Sant Cugat del Vallès
Barcelona - España / Spain

Certificado de análisis

Producto:	MEYPROGAT 90				
Código producto:	3000293			Lote:	1E0398
Cantidad:	1175000,000 G	Proveedor:	SOBERAL S.L.	Fecha fabricación:	10-2008
		Lote proveedor:	17171	Fecha retest:	10-2011

Determinaciones	Resultado	Especificaciones
RECEPCION COA	CONFORME	CERTIFICADO RECEPCIONADO

Fecha análisis: 10-05-2011 Especificación: 3000293 MEYPROGAT 90 (V) (gen/ver. 2/1)

Dictamen: CONFORME

Responsable Montse Planells

Certificado emitido electrónicamente, es válido sin firma

Cumple requerimientos de Ph. Eur.

Certificado_mmpp_FSIA_mt.rep / 20101214

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Fecha impresión / Print date: 30-09-2011

May 03 2011 2:33PM GRUPO FERRER 935044236 p.1

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First you add knowledge...

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info@danisco.com

Report number: 13195
800112081

Ferrer International
C. / Joan Buscalla 1-9
08190 SAN CUGAT DEL VALLES
Spanien

21-Mar-11

CERTIFICATE OF ANALYSES

Product	:	MEYPROGAT
Type	:	90
Order no.	:	800112081
Control no.	:	17171
P.O.	:	PE000345
Prod. date	:	Oct-10
Expiry date	:	Oct-11

Moisture (%)	:	7,0
Viscosity 1% after full hydration (mPa.s)	:	674
pH	:	6,2
Mesh +M150 (%)	:	0,6
Ash content (%)	:	1,3
Plate count	:	900
Moulds	:	10
Yeast	:	<50
Coliforms	:	neg.

Comments: The above mentioned typical analyses meet our issued specifications.

Cc.: Food

Signature: VG

ISO 9001 Danisco Zaandam B.V. Chamber of commerce File nr. 35007278

Annex 8. Product request form for Sutrilneo 5 mg pills.

ferrer

Departamento de Gestión Productos de Desarrollo

CIDF 0435 (1)

SOLICITUD / ENTREGA DE PRODUCTO

Nº SOLICITUD (a rellenar por GPD)
1110137

A rellenar por el solicitante

FECHA SOLICITUD	DEPARTAMENTO	SOLICITANTE	FIRMA
06 Oct. 11	ER-UAPA	JAUME SEUMA	[signature]

Código:		GF-009935-00
Producto:		SUTRILNEO (5 mg)
Número de lote:		E009
Peso Neto / unidades:		2 Comprimidos
Motivo:	Estudio nº :	UAPA – 1008-01
	Otros :	—
Observaciones:		Defensa patente cristalinidad Torasemida

Autorizado por:

Nombre	Firma	Fecha
Fabiano D'Aiolo	[signature]	4 Octubre 2011
Project Leader		

A rellenar por GPD

Documentación entregada con la sustancia:

- Certificado de análisis: ☐
- Ficha de seguridad: ☐
- Hoja de consumo de producto: ☐
- Otros (a especificar): ☐

Cantidad Entregada
2 comprimidos

Entregado por:

Nombre	Firma	Fecha
Abiú Lozano	[signature]	10/10/11
GPD		

A rellenar por el solicitante

Recibido por:

Nombre	Firma	Fecha
JAUME SEUMA	[signature]	10 Oct. 11
Solicitante		

COPIA AUTÉNTICA
Fecha: 10 Oct. 11
Firma: [signature]

Original in GPD

Code: Sutrilneo 5 mg
GF – 009935 – 00
Batch: E009
2 comprimidos

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signature

Dr. Antonio Guglietta
Typed or Printed Name

Dec 16, 2011
Date